Express Mail No.: EV 452 774 188 US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: RONALD J. PETTIS, et al.	Confirmation No.: 7814
Serial No.: 09/606,909	Art Unit: 3763
Filed: June 29, 2000	Examiner: Michael J. Hayes
For: INTRADERMAL DELIVERY OF SUBSTANCES	Attorney Docket No.: 11219-008-999 (500752-999007; P-4901)

DECLARATION OF DR. RONALD J. PETTIS
UNDER 37 C.F.R. § 1.132

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Dr. Ronald J. Pettis, do hereby declare and state:

1. I am a co-inventor of the subject matter disclosed and claimed in the above-identified patent application (herein referred to as the '909 application).

2. I am currently a Senior Scientist, at Becton, Dickinson and Company, Inc. which is the assignee of the '909 application.

3. My academic background, technical experience and list of publications are set forth in my *curriculum vitae*, attached hereto as Exhibit A.

4. I have been asked to comment on how the skilled artisan in the field of drug delivery could use the teachings of the '909 application to successfully deliver drugs with improved pharmacokinetic profiles.

5. By way of background, the pharmacokinetic profile of a drug may be assessed quantitatively by measuring and graphically plotting the serum concentrations of the drug over time. Typically, pharmacokinetic profiles are measured from the start of administration of the drug until the drug is cleared from the bloodstream. Measuring drug serum

concentrations will provide the following parameters: T_{max}, the time required for the drug to reach a maximum serum concentration; C_{max}, the maximum (or peak) serum concentration of the drug reached within a given dose and route of administration; T_{lag} (or "T_{onset}"), the delay time between the administration of a drug and the time for a measurable and detectable blood or plasma level of the drug; and the area under the serum concentration curve (AUC), which is a measure of bioavailability.

6. Pharmacokinetics is traditionally a comparative study, whereby the pharmacokinetic profile of a drug given at different doses or routes of administration may be compared by an inspection of the graphical representation of the profile. Different routes of administration typically include intravenous (IV), intramuscular (IM), and subcutaneous (SC) administration. For example, to achieve maximal C_{max} and bioavailability and minimal T_{max}, ideally drugs are injected directly into the vein, *i.e.*, intravenous administration (IV). However, IV injections are not practical, as they not only must be administered by a health care specialist, they depend on the skill level of that specialist. Intramuscular injections (IM) and subcutaneous injections (SC) have been used traditionally but routinely result in pharmacokinetic parameters that may not be as desirable as those obtained by the IV route. For example, SC or IM delivery typically results in a reduced plasma concentration of the drug, which ultimately has a direct bearing on its efficacy.

7. My co-inventors and I developed an intradermal (ID) drug delivery system that results in an improved pharmacokinetic parameters as compared to SC or IM delivery. This system, as described in the '909 application, involves inserting a needle into the subject's skin so that the needle penetrates the ID compartment and the needle's outlet depth and the exposed height of the outlet are located within the ID compartment. The substance is then delivered through the lumen of the needle by applying pressure in an amount effective to control the rate of delivery of the substance so that improved pharmacokinetic parameters are achieved relative to SC administration. Pressure is applied using any of the commonly known pressure generating devices, such as those disclosed in the '909 application (*e.g.*, pumps, syringes, elastomeric membranes, osmotic pressure or Belleville springs or washers) in an amount effective to control the rate of delivery of the substance. By controlling the rate of delivery of the substance into the ID compartment as described in the '909 application, improved pharmacokinetic parameters may be obtained, as compared to the pharmacokinetic parameters obtained via SC administration of the same substance.

8. As summarized below, the delivery of different substances into the ID compartment in accordance with the teachings of the '909 application results in improved pharmacokinetic parameters, regardless of the mode of application of the pressure (*i.e.* the actual pressure generating device), or the absolute value of the pressure applied, as long as the *rate of delivery was controlled and the needle was placed within the intradermal compartment.* The improved pharmacokinetic profile of the different substances delivered to the ID compartment is manifested as an improvement of two or more of the traditionally measured parameters that characterize the profile, *i.e.*, T_{max}, C_{max} or AUC.

9. The '909 application evidences that delivery of insulin to the ID compartment results in improved pharmacokinetic parameters, *i.e.*, increased C_{max} and AUC, as compared to delivery of insulin to the SC compartment. In Example 2 of the '909 application, insulin was administered to the ID compartment of a pig animal model (*see* the instant specification at page 7, line 25 to page 8, line 21). Insulin was delivered through the lumen of a hollow needle, having a total length of 2 mm, but designed such that the location of the needle outlet was 1 mm--within the ID compartment. Pressure was applied using an infusion pump and the rate of infusion delivery was controlled at a rate of 2U/hr. Blood samples were periodically withdrawn and analyzed for insulin concentration. The results are shown in Figure 4 (attached hereto as Exhibit B), where plasma insulin levels, subsequent to ID administration are plotted over time to generate a serum concentration – time curve (*i.e.,* its pharmacokinetic profile), which is compared to the pharmacokinetic profile observed for SC administration of insulin. It is clear from a visual inspection of Figure 4 that the *pharmacokinetic profile and parameters* of insulin delivered to the ID space is improved relative to that of SC delivery -- *i.e.*, a higher plasma level (increased C_{max}) and a higher bioavailability (increased AUC).

10. In another similar experiment, improved pharmacokinetic parameters were observed when human parathyroid 1-34 (PTH) was delivered to the intradermal compartment using the teachings of the invention. PTH was administered to the intradermal compartment of a pig animal model using a stainless 30 gauge such that the available length for skin penetration was 1-2 mm and the need outlet was at a depth of 1.7-2.0 mm in the skin when the needle was inserted and the total exposed height of the needle was 1-1.2 mm. Flow rate was controlled using a Harvard syringe pump, and PTH was infused for 4 hours at a rate of 75 µl/hr. As shown in Figure 3 of the '909 application (attached hereto as Exhibit C),

delivering PTH to the ID space results in an improved pharmacokinetic profile relative to that obtained by SC administration of PTH, *i.e.*, a faster T_{max}, an increased C_{max} and an increased AUC (the instant specification at p. 7, *ll.* 16-24; and Figure 4).

11. The two examples provided in the '909 application evidence that a substance can be delivered to the ID compartment under sufficient pressure to control the rate of delivery so that a desired pharmacokinetic profile is obtained. The desired profile may be an enhancement in two or more of the following parameters: T_{max}, C_{max} and AUC. In order to apply these teaching to other substances and formulations, one skilled in the art would deliver the substance to the ID compartment via a needle having an appropriate height and outlet depth as specified in the '909 application. One would utilize different pressures to control the rate of delivery. At the onset, a visual inspection of the delivery site to ensure bleb formation and a lack of leakage will be an effective initial indication of delivery to the ID compartment. Subsequent to delivery of the substance, blood samples are periodically drawn and analyzed for concentration of the substance. The results are plotted over time to generate a serum concentration time curve -- the pharmacokinetic profile -- which will provide one skilled in the art with sufficient information to assess if that pressure and rate of delivery are sufficient to provide the desired pharmacokinetic profile. This is indeed what was done in the following examples described in subsequent continuation-in-part applications.

12. For example, in a subsequent continuation-in-part application, U.S. Application Serial No. 09/893,746 ("the '746 application"), filed June 29, 2001, Example 1 shows that ID delivery of insulin results in an improved PK profile as compared to administration via the SC route, *i.e.*, an increased C_{max} and a decreased T_{max}. In Example 1 of the '746 application, insulin was infused in a swine model using a hollow single lumen microneedle (2 mm in length), designed such that the penetration of the needle outlet was limited to 1 mm. The insulin infusion was controlled using an insulin pump wherein the rate of delivery was 2 U/hr for 4 hours. As shown in Figure 1 of the '746 application (attached hereto as Exhibit D), the PK profile shows an increase in higher maximum plasma concentration and a decrease in T_{max} as compared to SC delivery.

13. Example VI of the '746 application shows that delivery of human granulocyte colony stimulating factor (GCSF) to the intradermal compartment of a Yucatan minipig results in an improved pharmacokinetic profile as compared to SC delivery. GCSF was delivered as a bolus using a dermal access design SS3_34 microdevice having a needle length

results in an improved pharmacokinetic profile as compared to SC delivery. GCSF was delivered as a bolus using a dermal access design SS3_34 microdevice having a needle length which places the needle within the ID compartment. Delivery rate was controlled via a Harvard syringe pump. As shown in Figure 6 of the '746 application (attached hereto as Exhibit E), ID delivery of GCSF resulted in a significantly faster T_{max} and a significantly higher AUC as compared to SC delivery (*see* pp. 30-31 of the '746 application, Figure 6).

14. In another continuation-in-part application, U.S. Application No. 10/028,988 ("the '988 application"), filed December 28, 2001, Example VIII shows that delivery of low molecular weight heparin, Fragmin®, to the intradermal compartment of a Yucatan minipig results in an improved pharmacokinetic profile as compared to SC delivery. Fragmin® was delivered as a bolus using a dermal access design SS3_34 microdevice having a needle length which places the needle within the ID compartment. Delivery rate was controlled via hand pressure from a glass microsyringe. As shown in Figure 8 of the '988 application (attached hereto as Exhibit F), ID delivery of Fragmin® resulted in a significantly increased C_{max} and a significantly higher AUC as compared to SC delivery (*see* pp. 32-33 of the '988 application, Figure 8).

15. I declare further that all statements made in this Declaration of my own knowledge are true, and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and that like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 19 of the United States code and that such willful false statements may jeopardize the validity of this application and any patent issuing thereon.

Dated: Jan 6th, 2005

Ronald J. Pettis

BD TECHNOLOGIES • 21 DAVIS DRIVE • RESEARCH TRIANGLE PARK, NC 27709
PHONE 919-597-6152 • FAX 919-597-6402 • E-MAIL RPETTIS@BD.COM

RONALD J. PETTIS

EDUCATION

1982 - 1986 Georgia Institute of Technology Atlanta, GA
B.S. Chemistry cum laude

1986 - 1988 University of North Carolina Chapel Hill, NC
M.S. Chemistry

1988 - 1991 University of North Carolina Chapel Hill, NC
Ph.D. Chemistry

PROFESSIONAL EXPERIENCE

1996 - Present BD Technologies RTP, NC
Senior Scientist, Team Leader-Therapeutic Drug Delivery
- Wesley J. Howe Award for Corporate Technology Innovation (2001)

1991 - 1996 University of North Carolina, School of Pharmacy Chapel Hill, NC
Research Fellow-Pharmaceutical Formulation and Delivery

PATENTS

6 issued and 17 pending US Patents:

United States Patent 6,722,364 April 20, 2004 *Medicament inhalation delivery devices and methods for using the same*

United States Patent 6,689,100 February 10, 2004 *Microdevice and method of delivering or withdrawing a substance through the skin of an animal*

United States Patent 6,656,147 December 2, 2003 *Method and delivery device for the transdermal administration of a substance*

United States Patent 6,607,513 August 19, 2003 *Device for withdrawing or administering a substance and method of manufacturing a device*

United States Patent 6,595,947 July 22, 2003 *Topical delivery of vaccines*

United States Patent 6,440,096 August 27, 2002 *Microdevice and method of manufacturing a microdevice*

PUBLICATIONS AND PRESENTATIONS

[redacted]
Atty. Docket No.: 11219-008-999
Serial No.: 09/606,909
Exhibit A

Pettis RJ, Knowles MR, Olivier KN, Kazantseva M, Hickey AJ. *Ionic interaction of amiloride and uridine 5'-triphosphate in nebulizer solutions.* J Pharm Sci. 2004 Sep;93(9):2399-406.

Mikszta JA, Alarcon JB, Brittingham JM, Sutter DE, Pettis RJ, Harvey NG. *Improved genetic immunization via micromechanical disruption of skin-barrier function and targeted epidermal delivery.* Nat Med. 2002 Apr;8(4):415-9.

Pettis RJ, Hall I, Costa D, Hickey AJ. *Aerosol delivery of muramyl dipeptide to rodent lungs.* AAPS PharmSci. 2000;2(3):E25.

Pettis RJ, Erickson BW, Forward RB, Rittschof D. *Superpotent synthetic tripeptide mimics of the mud-crab pumping pheromone.* Int J Pept Protein Res. 1993 Oct;42(4):312-9.

Pettis, R.J., Forward, R.B., Erickson, B.W., and Rittschof, D. (1993) *Superpotent Synthetic Tripeptide Mimics of the Mud-Crab Pumping Pheromone*, Int. J. Peptide Protein Res, 42:312-319.

Pettis, R.J., Middleton, B.A., Cho, M.J. (1994) *Preformulation studies of UCN-01: Solubility and stability enhancement by polyvinylpyrrolidone binding*, Pharm. Res., 11:S230.

Pettis, R.J., Becton, B.A., Cho, M.J., Tabibi, E. (1995) *Preformulation studies of sarcosine-chloroethylnitrosourea (SarCNU)*, Proc. Am. Assoc. Canc. Res., 36:311.

Atkins, K.M., Lalor, C.L., Concessio, N.M., Pettis, R.J., Hickey, A.J. (1995) *Aerodynamic size characterization, lung deposition and alveolar macrophage uptake of microparticulate suspension aerosols in guinea pigs, abstract*, 17th Annual Undergraduate Research Seminar, West Virginia University.

Lalor, C.J., Atkins, K.M., Concessio, N.M., Pettis, R.J., Hickey, A.J. (1996) *Lung deposition and alveolar macrophage uptake of microparticulates from suspension aerosols in guinea pigs*, abstract, Society of Toxicology 35th Annual Meeting, Anaheim, CA.

Pettis, R.J., Hickey, A.J. (1996) *Alveolar macrophage activation by muramyl dipeptide aerosols in guinea pigs*: Effects on cellular morphology, poster, AAPS Southeast Regional Meeting, Research Triangle Park, NC.

Pettis, R.J., Hickey, A.J. (1996) Effect of *muramyl dipeptide aerosols on guinea pig alveolar macrophages*, Pharm. Res., 13(9):S166.

Pettis, R.J., Knowles, M.R., Olivier, K.N., Hickey, A.J. (1996) *Ionic interaction of amiloride and uridine-5'-triphosphate (UTP) in solution*, Pharm. Res., 13(9):S179.

Pettis, R.J., Sutter, D., Dekker, J., Bock, R. (2000) *Microfabricated microneedles for disruption of skin barrier function*, poster, 2000 AAPS Annual Meeting and Exposition.

Mikszta, J. Alarcon, J. M. Brittingham, J. P. Dekker, R. J. Pettis, N. G. Harvey *Microdevice-Based Topical Delivery of DNA and Subunit Vaccines.*

AAPS PharmSci Vol. 2, No. 2, Abstract 2307 (2000)

Pettis, R.J., Haider, I., Mikszta, J., Alarcon, J., Brittingham, J.M., Davison, N., Solbrig, C., Zahn, J. (2001) *Hollow microneedle drug delivery systems: Biomechanical characterization and vaccine delivery*, AAPSPharmSci, Vol. 3, No. 3

Pettis, R.J., Harvey, N., Sutter, D., McFarland, A., Pollack, G., Leipmann, D., Zahn, J. (2002) *Intradermal insulin delivery via MEMS fabricated microneedles*, poster, 2002 AAPS Annual Meeting and Exposition,

Pettis, R.J., Kaestner, S., Sutter, D (2003) *Microneedle delivery of GCSF leads to unique pharmacokinetic advantages*, poster, 2003 AAPS Annual Meeting and Exposition, Salt Lake City, UH

Pettis, RJ, Kaestner, S, Sutter, D, Fentress, J, Harvey, N (2003) *Microneedle-Based Intradermal Delivery of Insulin to Diabetic Swine: A NovelParenteral Administration Method with Unique PK/PD Outcomes*, podium, 2003 CRS Annual Meeting, Honolulu, HA

PROFESSIONAL MEMBERSHIPS AND AFFILIATIONS

Member- Controlled Release Society

Member- American Association of Pharmaceutical Sciences

Member-Editorial Board, Drug Delivery Companies Report